REVIEW

Tuberculosis preventive therapy: An underutilised strategy to reduce individual risk of TB and contribute to TB control

G J Churchyard, R E Chaisson, G Maartens, H Getahun

Gavin Churchyard is Chief Executive Officer: Aurum Institute, Johannesburg, South Africa, and an Honorary Professor in the School of Public Health, University of the Witwatersrand, Johannesburg, South Africa. Richard Chaisson is Director: Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Gary Maartens is Professor and Chair of the Division of Clinical Pharmacology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa. Haileyesus Getahun is Coordinator, TB/HIV and Community Engagement, Global TB Programme, World Health Organization, Geneva, Switzerland.

Corresponding author: *G J Churchyard (gchurchyard@auruminstitute.org)*

Tuberculosis (TB) remains a global health problem, and South Africa (SA) has one of the world's worst TB epidemics. The World Health Organization (WHO) estimated in 1999 that one-third of the world's population was latently infected with TB. In SA up to 88% of HIV-uninfected young adults (31 - 35 years) are latently infected with TB. In the most recent meta-analysis, 6 - 12 months of isoniazid preventive therapy (IPT) was associated with a lower incidence of active TB than placebo (relative risk (RR) 0.68; 95% confidence interval (CI) 0.54 - 0.85), with the greatest benefit among individuals with a positive tuberculin skin test (TST) (RR 0.38; 95% CI 0.25 - 0.57). A clinical trial of IPT given with antiretroviral therapy (ART) for 12 months reduced TB incidence by 37% compared with ART alone (hazard ratio (HR) 0.63; 95% CI 0.41 - 0.94). The effect of IPT is limited in high-burden countries. IPT for 36 months v. 6 months reduced TB incidence among HIV-positive, TST-positive participants by 74% (HR 0.26; 95% CI 0.09 - 0.80). A study of more than 24 000 goldminers confirmed that IPT is safe, with only 0.5% experiencing adverse events. A meta-analysis of studies of IPT since 1951 did not show an increased risk of developing resistance. Alternative TB preventive therapy regimens, including high-dose isoniazid and rifapentine given weekly for 3 months, have been shown to have similar efficacy to IPT. Mathematical modelling suggests that scaling up continuous IPT targeted to HIV-positive persons, when used in combination with other treatment and prevention strategies, may substantially improve TB control.

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Burden of tuberculosis (TB) disease

TB remains a global health problem with an estimated burden of disease in 2012 of 8.6 million new cases, 13% co-infected with HIV, and an estimated 1.3 million TB deaths.[1] South Africa (SA) has one of the world's worst TB epidemics, with the highest TB incidence among the 22 highest TB burden countries in the world, estimated at 933/100 000 population in 2012, the third-largest absolute number of cases and the largest number of HIV-associated TB cases.[1] Approximately 65% of TB patients in SA are HIV-infected.[1]

Burden of latent TB infection (LTBI)

The World Health Organization (WHO) estimated in 1999 that one-third of the world's population is latently infected with *Mycobacterium tuberculosis*.[2] The greatest burden of LTBI is in South-East Asia (46%), the Western Pacific region (32%), Africa (31%) and the Eastern Mediterranean region (27%).[3] Sub-Saharan Africa, however, has the largest number of persons with LTBI who are co-infected with HIV. In high-transmission settings such as SA, up to 88% of HIV-uninfected young adults (31 - 35 years) are latently infected with TB, and 89% of SA goldminers are TB-infected.[4-7] These data suggest that the burden of LTBI in SA is enormous. The prevalence of tuberculin skin test (TST) positivity among people co-infected with HIV is estimated to be 22.8% overall and highest among those with $CD4^+$ counts ≥500 cells/μl (37.4%).[8] This is explained by the compromised ability of HIV-infected persons to react to the skin test because of cutaneous anergy associated with immunosuppression.

Risk of TB disease

LTBI occurs when individuals infected with *M. tuberculosis* harbour the organism in a latent state, characterised by slowed or intermittent metabolism and replication below the level necessary to produce clinical illness.[9] The lifetime risk of reactivation of latent infection in healthy HIV-uninfected individuals is 10%, with 5% developing TB during the first 2 - 5 years after infection. The risk is greatly increased in the context of immunosuppression, most notably due to HIV infection.[3] The WHO estimates that in countries with a generalised HIV epidemic, HIV-infected persons have a 20 - 37-fold greater risk of developing TB than HIV-uninfected persons. Although antiretroviral treatment (ART) reduces the risk of TB by approximately two-thirds,[10-12] TB remains a common cause of morbidity[13,14] and a leading cause of early mortality in individuals on ART.[15]

Purpose of this article

The purpose of this article is to present the evidence to support isoniazid preventive therapy (IPT) use, particularly continuous IPT (cIPT), in HIV-positive people as part of a combination of TB prevention strategies to reduce individual risk of TB and to contribute to TB control. Alternative TB preventive therapy regimens for

persons living with HIV and preventive therapy for HIV-uninfected persons at high risk of TB are also discussed. The paper focuses exclusively on TB preventive therapy for adults.

IPT in HIV infection

History of IPT in SA

The IPT guidelines for TST-positive people living with HIV were initially incorporated into the SA ART guidelines in 2005. Uptake of IPT was poor after introduction of these guidelines, largely due to TST creating a programmatic barrier to implementation and concerns of generating isoniazid resistance.[16]

In 2010, in line with the WHO recommendations, SA revised its national IPT guidelines and removed TST as a requirement to initiate IPT, to facilitate programmatic implementation of IPT. The uptake of IPT increased dramatically and more than 375 000 South Africans living with HIV were started on IPT in 2011 and 2012, respectively, making the IPT programme one of the largest in the world. Despite this, uptake of IPT among people living with HIV in care, including pregnant women, remains poor. The SA IPT guidelines were re-issued in 2013 and recommend at least 36 months of IPT for TST-positive HIV-infected persons, including people on ART; 6 months of IPT for those whose TST status is unknown, regardless of whether they are on ART or not; and 12 months of IPT for persons on ART if their TST is negative.[17] People living with HIV who are not on and do not require ART, and who have a negative TST, do not need IPT.

Screening for TB

Screening for active TB disease is required before commencing IPT to minimise the risk of developing drug resistance by inadvertently treating active TB with an inadequate regimen. An individual participant meta-analysis showed that a symptom screen of a cough (any duration), night sweats, loss of weight and fever was able to identify HIV-positive people with a very low probability of having undiagnosed active TB disease.[18] Chest radiography combined with symptom screening increased the sensitivity of TB screening, particularly among SA goldminers.[18-20] On the basis of these results, the WHO recommends that TB disease among people living with HIV be excluded before starting IPT, using a symptom screen of current cough, night sweats, fever and weight loss.[21] In HIV clinics that routinely screen their patients at every clinic visit, the WHO TB symptom screen performs less well, particularly among patients on ART.[22] In settings with a high prevalence of undiagnosed TB disease, some experts recommend excluding TB by doing a sputum culture or, in sick hospitalised patients, using a lateral flow assay for mycobacterial lipoarabinomannan on urine combined with Xpert MTB/RIF on sputum or urine.[22-24] TB screening before starting IPT may detect TB cases earlier, thereby reducing transmission and TB-associated mortality.

Efficacy of 6 - 12 months of IPT

In the most recent meta-analysis of people with HIV, 6 or 12 months of IPT was associated with a 32% lower incidence of active TB than placebo (relative risk (RR) 0.68; 95% confidence interval (CI) 0.54 - 0.85).[25] This benefit was greatest among individuals with a positive TST (RR 0.38; 95% CI 0.25 - 0.57).[25] IPT was also effective when implemented in a routine HIV care programme for SA goldminers, prior to ART availability.[26] IPT, given for 6 - 12 months after TB treatment, is effective in reducing the risk of recurrent TB disease and is recommended by the WHO.[21,27]

IPT with ART

IPT combined with ART reduced the risk of TB disease by 80 - 97% and death by up to 50% in HIV-infected persons.[28-31] A recent individually randomised, pragmatic, controlled trial demonstrated that IPT, taken for 12 months with ART, decreased TB incidence by 37% (hazard ratio (HR) 0.63; 95% CI 0.41 - 0.94) overall compared with ART alone.[32,33] The effectiveness of IPT was similar when assessed by interferon-gamma release assay and TST status.[33] The results of this study underpin the current SA guidelines for IPT with ART.

cIPT

Recent evidence from studies conducted in high-transmission settings suggests that cIPT may be beneficial. Among HIV-infected participants in Botswana who received 36 v. 6 months of IPT, TB incidence was reduced by 43% overall (HR 0.57; 95% CI 0.33 - 0.99); among TST-positive participants TB incidence was reduced by 74% (HR 0.26; 95% CI 0.09 - 0.80), whereas TST-negative participants received no benefit (HR 0.75; 95% CI 0.38 - 1.46).[31] In the per protocol analysis, there were no incident cases of TB among TST-positive persons who took 36 months of IPT. Among TST-positive, HIV-infected SA adults, incidence rates of TB or death were similar between participants who received cIPT or 6 months of IPT in the intention-to-treat analysis (2.7 v. 3.6/100 person-years, incidence rate ratio (IRR) 0.75; 95% CI 0.38 - 1.38).[34] In the per protocol analysis, the incidence of TB or death was reduced by 58% in the cIPT study arm, compared with the 6 months of IPT arm.

Durability of IPT

In the pre-HIV era, IPT was associated with a durable reduction in TB incidence in mental institutions and Alaskan villages.[35-38] In the HIV pre-ART era, 6 months of IPT in high-transmission settings was durable for up to 18 months.[39,40] In the ART era, IPT has limited durability in high TB transmission settings.[40,41] In the Botswana trial of 6 v. 36 months of IPT, among persons who took 6 months of IPT the risk of TB increased approximately 200 days after stopping IPT,[31] while among persons who took 36 months of IPT, TB incidence increased by 90% after stopping IPT.[42] Among SA goldminers, the incidence of TB in the intention-to-treat analysis was reduced by 58% during the intended 9-month IPT period. TB incidence increased rapidly following cessation of IPT and was similar to that observed for those who did not start IPT in the post-treatment period.[43]

Safety of IPT

The safety of IPT was recently confirmed in more than 23 500 SA goldminers. With clinical monitoring during the 9 months of IPT, the risk of isoniazid-associated adverse events, including clinical hepatitis, was low (0.5%), even among older patients and those on ART.[44] In the individually randomised trial of IPT with ART v. placebo with ART, participants on IPT were 2.13 times (95% CI 0.97 - 4.67) more likely to discontinue the study medication due to grade 3 adverse events or raised liver enzymes.[32] Among HIV-positive adults in Botswana, the risk of severe adverse events and death was similar in the 6-month and cIPT groups; however, the risk of death among persons with a negative TST was increased, although none of the deaths were attributed to isoniazid.[31] Among HIV-infected South Africans taking cIPT (v. 6 months of IPT), serious adverse reactions were more common (18.4 v. 15.4/100 person-years) as was permanent discontinuation of treatment (36.5% v. 1.9%).[34] Grade 3 or 4 elevation of aspartate or alanine aminotransferase during the treatment phase was much more common with cIPT than with 6 months of IPT (28.0% v. 5.5%; $p<0.001$).[34]

Isoniazid resistance

Theoretically, if active TB is missed and the bacterial load is large enough, treatment with monotherapy or an inadequate regimen has the potential to generate drug resistance. A systematic review of

studies of IPT conducted between 1951 and 2005 concluded that IPT was not associated with an increased risk of isoniazid resistance and that isoniazid resistance is much more likely to result from inadequate treatment of active disease.[45] The studies of cIPT in Botswana and SA did not show an increased risk of isoniazid resistance.[31,34] Among 126 goldminers with TB after starting IPT, the prevalence of isoniazid resistance and treatment outcomes were similar to those in TB cases without previous exposure to IPT.[46] The impact of wide-scale uptake of preventive therapy on generating drug resistance is unknown. Mathematical modelling suggests that the emergence of isoniazid resistance with IPT use may be reduced by delivering IPT to those who will benefit the most and by improved case finding and prompt treatment of those with drug-resistant TB disease.[47,48]

Population-level effect of IPT

In the pre-HIV era, community-wide IPT was evaluated in Alaska, Greenland and Tunisia, all of which had epidemic TB. In Alaska, IPT was given to households for 1 year, which reduced the risk of TB by 69%.[35] As the intervention was so successful, 12 months of IPT was given to both placebo and IPT groups 5 years later, and the population-level effect has been durable for more than 3 decades.[36] In Greenland and Tunisia, the effect of community-wide IPT was modest (31% and 26% reduction in TB incidence, respectively), largely owing to an inadequate dose of isoniazid and/or poor adherence to IPT in both of the trials.[49,50] The Thibela TB study[51] evaluated the effectiveness of community-wide IPT in addition to standard of care, compared with standard of care alone, among SA goldminers. The intervention, which is unprecedented in the history of TB control, included mass screening for TB using chest radiography and symptoms, simultaneously linked to treatment for active disease or latent infection. Despite reducing the individual risk of TB by 58% while participants took the 9-month course of IPT, the effect waned soon after stopping IPT and there was no measurable reduction in TB incidence or prevalence at a population level after the intervention was completed.[43] Mathematical modelling suggested that even if the intervention was optimally implemented, a 20% reduction in TB incidence at a population level was the most that could be expected.[51] The modelling also suggested that cIPT would have a profound impact on TB incidence at a population level.[51]

TB after IPT: Possible mechanisms

TB that occurs after IPT may be due to reactivation of inadequately treated TB or reinfection with a new strain of TB. Isoniazid impairs mycobacterial wall synthesis and is a potent bactericidal drug that results in a rapid decline in actively multiplying mycobacteria. A recent study showed that isoniazid rapidly killed actively dividing *M. smegmatus*. However, a few cells continued to divide in the presence of isoniazid owing to dynamic persistence associated with stochastic pulsing of catalase-peroxidase (KatG), which activates isoniazid.[52] When isoniazid was withdrawn, the surviving cells underwent exponential growth again and were susceptible to isoniazid when it was reintroduced, suggesting that they had not developed resistance to the drug. It is likely that a similar phenomenon occurs when *M. tuberculosis* is treated with isoniazid. In support of this hypothesis, mathematical modelling of the Thibela TB intervention was not able to mirror the observed data unless the model assumed that IPT does not cure LTBI. If the model is correct and IPT does not cure LTBI, reactivation of inadequately treated LTBI after stopping treatment may in part explain the lack of durable benefit. In high-transmission settings, reinfection with a new strain of TB has been shown to be an important cause of recurrent TB disease after successful completion of treatment in HIV-infected and HIV-uninfected TB patients.[53,54] In settings with a high annual risk of infection such as SA (estimated at 4.7% per year), it is likely that reinfection will contribute to the limited durability of IPT. In high-burden settings, both reactivation of inadequately treated LTBI and reinfection are likely to limit the durability of IPT. Regardless of the mechanism of TB after IPT, cIPT will reduce the risk of TB in persons living with HIV.[31,42]

Alternative TB preventive therapy regimens

Efficacy of alternative preventive therapy regimens

Alternative TB preventive therapy regimens have also been evaluated in people living with HIV. A meta-analysis of TB preventive therapy regimens found rifampicin-containing regimens (rifampicin and pyrazinamide; isoniazid and rifampicin; isoniazid, rifampicin and pyrazinamide) not to be more effective than IPT alone.[25] In the pre-ART era, however, the rifampicin-based regimens were shown to have a more durable effect than isoniazid alone.[40,41]

A novel regimen of intermittent high-dose isoniazid and rifapentine given weekly for 3 months has recently been evaluated in low and high TB burden settings. Rifapentine is a rifamycin with a long half-life and greater potency against *M. tuberculosis* than rifampicin. In mouse models of LTBI, rifapentine had a greater sterilising effect than isoniazid,[55] and weekly high-dose rifapentine and isoniazid for 3 months (3HP) had greater efficacy than isoniazid alone.[56] The TB Trials Consortium Study 26[57] compared 3 months of high-dose once-weekly isoniazid (900 mg) and rifapentine (900 mg) (3HP) with 9 months of daily isoniazid (300 mg) (9H) in a non-inferiority study design.The study was conducted in low to medium TB and HIV burden settings (USA, Canada, Brazil and Spain). Eligible participants aged 2 years and above were enrolled into the study, regardless of HIV status. The study showed that 3HP was non-inferior to 9H in the modified intention-to-treat and per protocol analysis, and there was a trend towards superiority in reducing TB incidence (9H: 16/100 person-years; 3HP: 7/100). The 3HP study arm had a higher treatment completion rate than the 9H arm (82% v. 69%).[57] As few HIV-infected persons were enrolled into Study 26 (2.6% HIV-infected), an ancillary study was conducted to evaluate safety, tolerability and efficacy of 3HP in HIV-infected adults. Among 399 HIV-infected persons (193 9H, 206 3HP), 3HP was non-inferior to 9H, with cumulative TB incidences in the 3HP v. the 9H arm of 1.01 and 3.69/100 person-years, respectively.[58,59] 3HP compared with 9H in HIV-infected persons was tolerable and had higher completion rates (88% v. 64%).[58,59]

The 3HP regimen was also compared with 6 months of IPT (6H) in HIV-infected, ART-naive (at enrolment), TST-positive SA adults. In the intention-to-treat analysis, the incidence rates of active TB or death in the 3HP and 6H arms were similar (3.1 v. 3.6/100 person-years, respectively, crude IRR 0.87 (95% CI 0.54 - 1.39)).[34] Based on the results of TB Trials Consortium Study 26, the US Centers for Disease Control (CDC) issued recommendations for the use of the 3HP regimen for the treatment of LTBI.[47] The CDC is currently evaluating self-administered, as opposed to directly observed, 3HP.

Safety of alternative preventive therapy regimens

Rifampicin-based regimens (rifampicin and pyrazinamide; isoniazid and rifampicin; isoniazid, rifampicin and pyrazinamide), compared with IPT, in people with HIV are associated with a greater rate of treatment discontinuation due to adverse effects.[25] In Study 26 participants, the vast majority of whom were HIV-uninfected, there was reduced drug-related hepatotoxicity in the 3HP study arm

compared with the 9H arm (0.4% v. 2.7%), but rates of permanent discontinuation due to an adverse event were higher (4.9% v. 3.7%).[57] In the follow-on trial to Study 26 among HIV-infected persons taking 3HP v. 9H, the rates of drug discontinuation due to adverse drug reactions were similar (3.4% v. 4.2%).[58,59] Among HIV-infected, TST-positive adult South Africans taking 3HP v. 6 months of IPT, grade 3 or 4 hepatotoxicity (elevated alanine or aspartame aminotransferase) occurred less commonly in the 3HP study arm (1.5% v. 5.5%, respectively), and the rates of permanent discontinuation of the study drug were similar (1.8% v. 1.9%, respectively).[34]

TB preventive therapy for HIV-uninfected persons at high risk of TB

TB preventive therapy is recommended for HIV-uninfected persons who are receiving chemotherapy or anti-tumour necrosis factor (TNF) therapy and are at increased risk of developing TB. The South African Rheumatism and Arthritis Association recommends a regimen of either isoniazid or rifampicin for 3 months or IPT for 6 - 9 months for TST-positive persons prior to starting anti-TNF drugs. Silicosis is an occupational lung disease that results from chronic silica dust exposure and is associated with an approximately threefold greater risk of TB than in silica-exposed workers who do not have silicosis. The National Department of Health has included recommendations for HIV-uninfected persons with silicosis in the 2013 IPT guidelines: 36 months of IPT if TST-positive; 6 months IPT if TST unknown; no IPT if TST-negative. For people living with HIV and silicosis, the IPT guidelines for people living with HIV should be followed.

Combination TB prevention: The role of IPT

The WHO recommends IPT for people living with HIV as part of a combination of TB prevention strategies that include infection control to reduce exposure to TB, intensified case finding to detect cases earlier, and ART to reduce vulnerability to TB, in addition to reducing the numbers lost to follow-up prior to starting TB treatment and reducing the time to starting TB treatment.[21,60-62] However, implementation of these strategies has been poor. Mathematical modelling has suggested that high coverage of IPT, particularly if it is given continuously and in combination with other treatment and prevention strategies, will contribute to TB control and accelerate progress towards elimination of the disease.[51,63,64]

Conclusion

IPT is safe, does not generate isoniazid resistance, and reduces the risk of TB among persons living with HIV, particularly if given continuously to those with evidence of TB infection. Continuous IPT should be used in combination with other TB treatment and prevention strategies to contribute to TB control. Alternative TB preventive therapy regimens may be considered for certain patients at high risk of TB.

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This month in the *SAMJ* ...

Jenny Edge,[*,†] guest editor for CME this month, is a general surgeon with a particular interest in the management of breast diseases. She completed her undergraduate training at University College Hospital, London, also undertaking an intercalated BSc in Anthropology and graduating BSc, MBBS. She went on to pursue an FRCS and MMed (Surg), undertaking her surgical training at Stellenbosch University. She worked in the UK and New Zealand before joining her husband in South Africa. She now works at the Christiaan Barnard Memorial Hospital and is an honorary lecturer at the University of Cape Town.

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† Edge J. Breast Cancer. S Afr Med J 2014;104(5):376. [http://dx.doi.org/10.7196/SAMJ.8262]

Gavin Churchyard*** is a specialist physician and founder and Chief Executive Officer of the Aurum Institute, an independent, not-for-profit, proudly South African public benefit organisation that focuses on tuberculosis and HIV service delivery, management and research. He is an honorary professor at the School of Public Health, University of the Witwatersrand, Johannesburg, and at the Faculty of Epidemiology and Population Health, Department of Infectious Diseases, London School of Hygiene and Tropical Medicine. Prof. Churchyard is Chair of the World Health Organization (WHO) Task Force for the Development of New Policies for the Treatment of TB and a member of the WHO Strategic Technical Advisory Group for TB. He is Vice-Chair of the NIH/DAIDS-funded AIDS Clinical Trials Group (ACTG) Network and the Transformative Science Group for TB, and Chair of the ACTG Host Directed Therapy for TB Working Group.

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